NOVEL USE AND METHOD OF RAPAMYCIN TO TREAT TOXIC SHOCK

[0001] CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0002] This application claims priority from U.S. Provisional Application No. 61/231,348, filed on Aug. 5, 2009, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] Work related to the present invention had U.S. government support under Grant No. 3.10035_07_RD-B, awarded by Defense Threat Reduction Agency to Teresa Krakauer. The government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[0004] The present invention relates to the treatment of toxic shock syndrome. More specifically, the invention relates to the utilization of rapamycin for treating toxic shock induced by *staphylococcal* and *streptococcal* exotoxins.

[0005] Documents cited in this description are denoted numerically, in parenthetical, by reference to a bibliography below.

[0006] *Staphylococcal* exotoxins are among the most common etiological agents that cause toxic shock syndrome (34-35, 44, 52). The disease is characterized by fever, hypotension, desquamation of skin, and dysfunction of multiple organ systems (8, 49). These toxins bind directly to the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells and subsequently stimulate T cells expressing specific Vβ elements on T-cell receptors (9, 15, 25, 35, 41, 50). *Staphylococcal* enterotoxin B (SEB) and the distantly related toxic shock syndrome toxin 1 (TSST-1), are also called superantigens because they induce massive proliferation of T cells (35). In vitro and in vivo studies show that these superantigens induce high levels of various proinflammatory cytokines and these potent mediators cause lethal shock in animal models (1, 6, 23, 29, 39, 43, 46, 53, 58, 62).

[0007] SEB also causes food poisoning (4, 22, 59) and is a potential bioterrorism threat agent, as humans are extremely sensitive to this superantigen, especially by inhalation (34). There is currently no effective therapeutic treatment for SEB-induced shock except for the use of intravenous immunoglobulins (IVIG) (11). However IVIG is protective only when administered concurrently with SEB or soon after SEB exposure (32). Various in vitro experiments identified inhibitors to counteract the biological effects of SEB, only some of which were successful in ameliorating SEB-induced shock in experimental models (1, 26, 27, 29, 31, 58).

[0008] The gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pyogenes* also produce a number of other superantigens which share a common three-dimensional structure and similar biological activities (16, 30, 45). *Staphylococcal* enterotoxin (SEA), TSST-1, *streptococcal* pyrogenic exotoxin A (SPEA) and *streptococcal* pyrogenic exotoxin C (SPEC) also bind to MHC class II molecules and specific Vβ elements on T-cell receptors on host cells (16, 36, 44). Many of the biological effects of these bacterial pyrogenic superantigens are similar in vitro and in vivo. The common structure and mechanism of action of bacterial superantigens often produce the same pathology and diseases.

[0009] In some prior studies, therapeutic agents had to be administered before SEB exposure to achieve protective effects (1, 33).

[0010] Rapamycin is a relatively new FDA-approved drug used to prevent graft rejection in renal transplantation, as it shows less nephrotoxicity than calcineurin inhibitors (7, 14, 47, 48, 56). Recent studies reveal other uses in animal models of cancer (24), diabetic nephropathy (42), bleomycin-induced pulmonary fibrosis (37), liver fibrosis (5) and tuberous sclerosis (38). Rapamycin binds intracellularly to FK506-binding proteins, specifically FKBP12, the rapamycin-FKBP12 complex then binds to a distinct molecular target called mammalian target of rapamycin (mTOR) (40, 56). Other studies identified the mTOR as the conserved serine-threonine kinase for sensing cellular stress and rapamycin promotes anabolic cellular processes in response to stress signals (21, 55, 57, 61). The mTOR pathway regulates myogenesis (13), cell cycle arrest (17, 21), adipocyte differentiation (3), and insulin signaling (55, 57). The immunological effects of rapamycin include regulation of T-cell activation (56), differentiation, expansion, and preservation of regulatory T cells (2, 10, 20, 54), downregulation of dendritic cells (12, 60), and GM-CSF-induced neutrophil migration (18).

[0011] There is a need to develop a treatment for toxic shock syndrome. In view of the potent immunosuppressive effects of rapamycin, the therapeutic impact of rapamycin on toxic shock is investigated.

SUMMARY OF THE INVENTION

[0012] It is an object of the present invention to provide a new approach to treating toxic shock syndrome, particularly toxic shock induced by *Staphylococcal* exotoxins.

[0013] Accordingly, the present invention provides, in one aspect, a method for preventing or treating toxic shock by administering a therapeutically effective amount of an agent to a subject exposed to a toxin. In one embodiment, the agent is rapamycin.

[0014] In another embodiment, the toxic shock is induced by *Staphylococcal* enterotoxin A (SEA), *Staphylococcal* enterotoxin B (SEB), toxic shock syndrome toxin 1 (TSST-1), *streptococcal* pyrogenic exotoxin A (SPEA), or *streptococcal* pyrogenic exotoxin C (SPEC).

[0015] In yet another embodiment, rapamycin is administered to a subject in less than 24 hours, less than 23 hours, less than 22 hours, less than 21 hours, less than 20 hours, less than 19 hours, less than 18 hours, less than 17 hour, less than 16 hours, less than 15 hours, less than 14 hours, less than 13 hours, less than 12 hours, less than 11 hours, less than 10 hours, less than 9 hours, less than 8 hours, less than 7 hours, less than 6 hours, less than 5 hours, less than 4 hours, less than 3 hours, less than 2 hours, or less than 1 hour following exposure to a toxin.

[0016] In another embodiment, rapamycin is administered to a subject prior to exposure to a toxin. For example, rapamycin administered at 30 minutes to 1 hour prior to exposure to a toxin is expected to achieve the therapeutic effects.

[0017] In some embodiments, more than one dose of rapamycin is administered to a subject during a period of up to 96 hours following exposure to a toxin at an interval of every 24 hours. In one embodiment, the interval is every 12 hours,